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Comparison of various clinicopathological parameters with a depth of invasion in basal cell carcinoma

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Abstract

Basal cell carcinoma (BCC) which is the most widespread malignant skin tumor around the world is an increasingly important public health problem since the incidence of BCC increases worldwide. In our study, we purposed to measure the variability of BCC invasion depth according to subtype, age, tumor diameter, gender, lymphocytic response, and anatomical localization and contribute to similar studies.100 BCC cases diagnosed in our department of pathology between January 2018 - June 2021 were included in the study. Clinicopathological parameters of the cases, such as demographic findings, tumor diameter, anatomical localization, histological type, and lymphocytic response, were obtained from the automatic data recording system of the hospital. The mean invasion depth was 3±1.87(0,5-13) mm. The relationship between depth of invasion and histopathological subtype (p=0.370), age (p=0.405), gender (p=0.937), lymphocytic response (p=0.418), and anatomical localization (p=0.118) was not significant. The depth of invasion was found to increase as the tumor diameter increases (p=0.004). A progressive increase in the incidence of BCC is noted making it an occupational and environmental disease with an obvious impact on the life quality of the patients. This puts a notable burden on the healthcare system, particularly in cases of invasive treatments and post-treatment relapses. Conducting multicenter research that investigates the efficacy of depth of invasion in different anatomical locations in a higher number of cases may help develop more effective treatments.

Keywords: Basal cell, carcinoma, histopathologic subtype, invasion

Introduction

BCC is the most widespread malignant skin tumor around the world and BCCs account for approximately 90% of most skin tumor series [1]. The incidence of UV-induced skin cancers, including BCC, increases worldwide, which makes it an increasingly important public health problem. Although mortality rates of BCC are low, localized tissue invasion can cause significant cosmetic and functional morbidity, as most lesions are localized on the face. The BCC results occur as a result of a combination of environmental and genetic factors. In particular, most of the genes contribute to the pathogenesis of BCC contain a mutation related to UV-induced DNA damage [2-4]. BCC is most commonly seen in fair-skinned individuals, usually as a single lesion, but may develop as multiple lesions as well [5]. Age is another important risk factor. Lifelong immunosuppressive therapy is among the other risk factors. It is known that the risk of BCC increases in patients that receive immunosuppressive therapy because of solid organ transplantation [6]. BCC has many subtypes. Various BCC subtypes have been classified by different growth patterns by the World Health Organization (WHO) in 2018. The BCC's histological subtypes are divided into two groups by the recurrence risk. While basosquamous carcinoma, infiltrating BCC, sclerosing/morpheic BCC, micronodular BCC, and BCC with sarcomatoid differentiation are included in the high-risk group, superficial BCC, infundibulocystic BCC, nodular BCC,

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pigmented BCC, and fibroepithelial BCC constitute the low-risk group [4,5]. The tumor may be one subtype of BCC or a combination of multiple subtypes. Certain subtypes tend to appear in certain parts of the body. The most effective and common treatment method is surgical excision [2,7]. For low-risk tumors for which surgery is not considered, other treatment methods are electrodesiccation, cryotherapy, topical immunostimulants such as imiquimod or 5 fluorouracil, and photodynamic therapy [8].

Nowadays, not much is known about the variation of depth of invasion in BCC subtypes by anatomical location. It is thought that understanding of the invasion depth in BCC subtypes according to different anatomical locations will lead to better clinical management [9]. In addition, a recent study found that gender and region do not correlate with invasion depth in BCCs [10].

The aim of our study is to examine the variability of the depth of invasion in BCC by subtype, age, tumor diameter, gender, lymphocytic response, and anatomical location and contribute to similar studies.

Material and Methods

100 BCC cases diagnosed in our department of pathology between January 2018 - June 2021 were included in the study. Data of the cases, such as demographic findings, tumor diameter, anatomical localization, histological type, and lymphocytic response, were obtained from the automatic data recording system of the hospital. The cases were re-analyzed by two pathologists experienced in dermatopathology and divided into histopathological subtypes according to the 2018 WHO Classification. After histopathological analysis, the BCC cases were separated into one of the following categories: superficial, micronodular, nodular, nodulocystic, adenoid, and infiltrative. Cases involving multiples subtypes were included in the subtype category that constituted more than 50% of the tumor (if there was no subtype meeting the >50% requirement, these cases were excluded). Tumor diameters were measured macroscopically before tissue processing. Depth of invasion was the maximum tumor thickness, measured in increments of 0.1 mm, indicated by a vertical line from the granular layer in the epidermis, if ulcers, from the ulcer base to the deepest tumor cells [9]. (Figure 1) Cases at the base surgical margin were excluded from the study. Breslow thickness in malignant melanoma was used for the degree of depth of invasion (DDI). It was categorized as 1:<0.8mm, 2:0.8-1mm, 3:1-2mm, 4:2-4mm, and 5:>4mm. The anatomical level was based on the Clark Level in malignant melanoma. The invasions were categorized as follows: lesions limited to the epidermis: level I, invasion of the lesion into the papillary dermis: level II, invasion of the lesion to the papillary-reticular-dermal interface: level III, invasion of the lesion into the reticular dermis: level IV, and invasion of the lesion into the subcutaneous adipose tissue: level V [11].

The density of lymphocytic infiltration was recorded as follows: no inflammatory infiltrate:0, scattering, clumps of infiltrating cells surrounding <25% of the tumor, sparse infiltrate:1, inflammatory cell clumps surrounding 25%-75% of the tumor, moderate infiltrate:2, and the dense infiltrate surrounding >75% of the tumor and/or forming a lymphoid follicle was recorded as 3 [11]. (Figure 2)

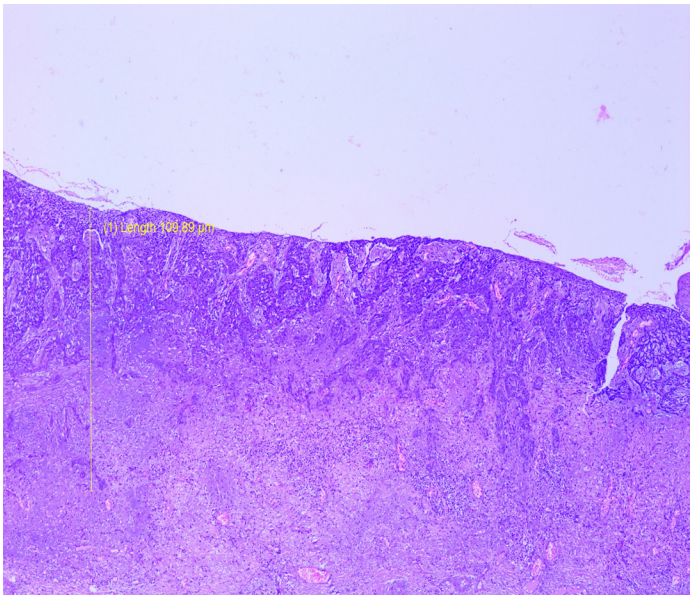

Figure 1. Depth of invasion in infiltrative BCC. H&E, X20

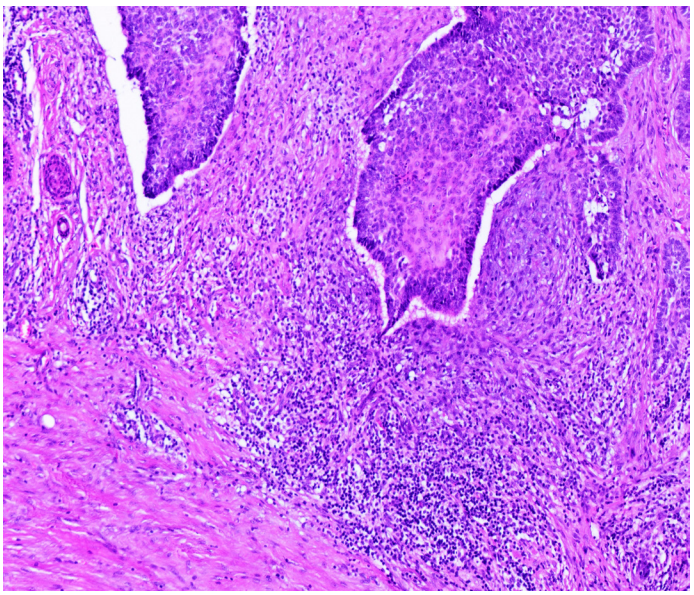

Figure 2. Lymphocytic response in BCC. H&E, X100

IBM SPSS (version 25.0 for Windows) was refered to conduct all analyses. In the present study the variables of interest were expressed as either mean±the standard deviation or the percentage, depending on the most appropriate to describe the data. Chi-square tests or one-way analysis of variance (ANOVA) was applied to compare the data. $p<0.05$ was noted to be significant.

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The study was approved by KTO Karatay University Ethics Committee (approval number:2021/025).

Results

The mean depth of invasion was 3±1.87(0.5-13) mm. The mean ages of the cases were 63.9±6.7 years in females and 66.2±15.8 years in males. In terms of DDI levels, 14% of the cases were level 1, 25% was level 2, 38% was level 3, 9% was level 4, and 14% was level 5. The mean age of the cases with DDI level 1 was found to be 63.86±19.58 years, it was found to be 64.16±20.45 for level 2 patients, 62.45±12.20 for level 3 patients, 70.78±12.46 for level 4 patients, and 70.93±16.27 for level 5 patients. The relationship between age and DDI was not significant (p=0.405).

6% of the cases were located on the scalp, 6% on the peroral, 10% on the forehead, 5% on the malar, 28% on the nose, 6% on the body, 8% on the ear, 6% on the nasolabial, 18% on periorbital, and 7% on the cheek. The distribution of DDI levels by localization is given in Table 1. The relationship between DDI and anatomical localization of the tumor was not significant (p=0.118).

The distribution of the depth of invasion by gender is given in Table 2. The relationship between gender and depth of invasion was not significant (p=0.937).

The relationship was not found between DDI and the anatomical level (p=0.06), recurrence (p=0.107), and histopathological subtypes (p=0.24). The distribution of subtypes by DDI is given in Table 3. Other variables and clinicopathological features are summarized in Table 4.

Mean tumor diameter was found to be 0.8±0.6 in DDI level 1 cases, 0.7±0.4 cm in level 2 cases, 1.0±0.5 cm in level 3 cases, 1.0±0.4 cm in level 4 cases, and 1.6±0.8 cm in level 5 cases. It was found that the depth of invasion increased as the tumor diameter increased (p=0.001). A significant relationship was not found between tumor diameter and histopathological subtype (p=0.370).

There was no correlation between the lymphocytic response to the tumor and DDI (p=0.418) and age (p=0.326).

Table 1. Distribution of degree of the depth of invasion by anatomical localization

DDI*	Anatomical localization (%)										P-value
	Scalp (n=6)	Peroral (n=6)	Forehead (n=10)	Malar (n=5)	Nose (n=28)	Body (n=6)	Ear (n=8)	Nasolabial (n=6)	Periorbital (n=18)	Cheek (n=7)	
1	1 (7.1)	1 (7.1)	1 (7.1)	2 (14.3)	4 (28.6)	4 (28.6)	-	-	1 (7.1)	-	0.118
2	1 (4)	2 (8)	2 (8)	1 (4)	7 (28)	1 (4)	4 (16)	-	5 (20)	2 (8)	
3	3 (7.9)	1 (2.6)	5 (13.2)	-	12 (31.6)	-	2 (5.3)	4 (10.5)	7 (18.4)	4 (10.5)	
4	-	2 (22.2)	-	1 (11.1)	2 (22.2)	1 (11.1)	-	1 (11.1)	2 (22.2)	-	
5	1 (7.1)	-	2 (14.3)	1 (7.1)	3 (21.4)	-	2 (14.3)	1 (7.1)	3 (21.4)	1 (7.1)	

*:Degree of the depth of invasion. 1:<0.8mm, 2:0.8-1mm, 3:1-2mm, 4:2-4mm, and 5:>4mm

Table 2. Distribution of depth of invasion by gender

DDI*	Gender(%)		P-value
	Female (n=54)	Male (n=46)	
1	7 (13)	7 (15.2)	0.937
2	13 (24.1)	12 (26.1)	
3	20 (37)	18 (39.2)	
4	6 (11.1)	3 (6.5)	
5	8 (14.8)	6 (13)	

*:Degree of the depth of invasion. 1:<0.8mm, 2:0.8-1mm, 3:1-2mm, 4:2-4mm, and 5:>4mm

Table 3. Distribution of subtypes by degree of depth of invasion

DDI*	Histopathological subtypes (%)						P-value
	Nodulocystic (n=9)	Nodular (n=38)	Micronodular (n=21)	Superficial (n=4)	Adenoid (n=12)	Infiltrative (n=16)	
1	-	5 (35.7)	4 (28.6)	4 (28.6)	-	1 (7.1)	0.24
2	5(20)	7 (28)	5 (20)	-	2 (8)	6 (24)	
3	1 (2.6)	18 (47.4)	7 (18.4)	-	7 (18.4)	5 (13.2)	
4	2 (22.2)	2 (22.2)	2 (22.2)	-	1 (11.1)	2 (22.2)	
5	1 (7.1)	6 (42.9)	3 (21.4)	-	2 (14.3)	2 (14.3)	

*:Degree of the depth of invasion. 1:<0.8mm, 2:0.8-1mm, 3:1-2mm, 4:2-4mm, and 5:>4mm

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Table 4. Clinicopathological Characteristics of 100 Patients with BCC

Variable	Number of patients (%)
Age (years)	
≤65	50 (50)
>65	50 (50)
Mean	65±16.21(22-103)
Anatomic level	
1	1(1)
2	2(2)
3	16(16)
4	56(56)
5	25(25)
Tumor size(cm)	
≤1	59(59)
>1 but not >2	32(32)
>2	9(9)
Lymphocytic response	
0	0
1	21(21)
2	38(38)
3	41(41)
Degree of depth of invasion	
1	14(14)
2	25(25)
3	38(38)
4	9(9)
5	14(14)
Recurrence	
Yes	10(10)
No	90(90)

Discussion

BCC is the most widespread cancer in humans. It was first defined in 1824 by Jacob and identified as basal cell epithelioma [4,12]. BCC accounts for 70-90% of all skin cancers [1,8]. Ultraviolet rays are the most important risk factor for skin malignancies, involving BCC. It most commonly occurs in the head and neck region [5,7].

BCC affects older men (>60 years old) and younger women (<40 years old) more [2,7]. This may be because the exposure of men and women to the sun differs according to their type of jobs, clothing, and other regional customs [7]. We also observed that male patients in our series were older than female patients. Pyne et al. revealed that tumor invasion for BCCs was deeper in male patients compared to female patients. In this study, nonetheless, we did not detect a remarkable relationship between gender and age and tumor invasion [9].

Nodular BCC types, followed by superficial and infiltrative BCC types, are the most commonly seen histopathological subtypes [5]. In our cases, nodular (38%), micronodular (21%), and infiltrative (16%) types were more prominent. Contrary to the findings in the literature, the second most common type in our study was micronodular BCC.

Of all BCC subtypes, nodulocystic BCCs have the longest depth of invasion and the largest tumor diameter [5]. There are other studies stating that the deepest tumors are nodulocystic and nodular BCC subtypes [9]. In this study, we did not detect a significant relationship between histopathological subtypes and depth of invasion. However, regardless of the histopathological subtypes, we observed that the depth of invasion increased as the tumor diameter increased.

In the study by Flohil et al., which reported that age-standardized BCC for all body regions, incidence rates increased significantly, and head and neck area was found to be the most affected region both in men and women [2]. While it was observed that more than 58% of newly diagnosed BCCs were localized in the head and neck region in 2009, 94% of the tumors in our cases were located in the head and neck region.

A study, which found that head and neck BCCs have a higher depth of invasion compared to those in the body and limb regions, also found an increase in mean tumor depth in both the upper and lower extremities for the distal regions compared to the proximal limb regions [9]. In this study, no significant relationship between anatomical localization and anatomical level and depth of invasion was observed. The reason for this difference may be due to the head localization of most of our cases. In many studies, it has been revealed that total skin thickness, epidermis, and dermis thickness vary according to age, gender, ethnicity, and different body regions. It is known that the thinnest skin thicknesses are in the eyelids, whereas publications are claiming that the dermis is thicker in the shoulders, sternum, earlobes, upper arms, and cheeks [13]. The study of Oltulu et al. also supports this claim. Differences in total skin thickness according to anatomical localizations may be related to the depth of invasion and anatomical level [14]. Future studies involving more BCC cases in different body regions may further shed light on this issue.

Tumor immunogenicity is increasingly recognized as an important factor in tumor progression, and a better understanding of its ability to evade the host anti-tumor response is needed to improve treatment methods. The cancer immune surveillance theory describes the continuous interaction between tumor survival tactics and the host anti-tumor response [15]. The presence of increased lymphocyte infiltration in the tumor periphery and the high risk of immunocompromised individuals indicate that BCC is an immunogenic tumor. Aging with immunosuppression and/or associated reduction in immunity may be an important factor in the development, number, and aggression of BCC [10]. Based on these, we compared the age and depth of invasion with the lymphocytic response to the tumor, but we did not find a statistically significant relationship. Immunotherapy is being developed as a promising treatment strategy for several types of cancer, where topical immunostimulants are among the possibilities

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for superficial BCC [8]. While treatment recommendations are given in accordance with diameter and subtype, there are no similar recommendations based on the depth of invasion in the current literature. However, in any topical treatment, adequate penetration of a drug into the target is crucial. The relationship between depth of invasion and therapeutic response to topical agents has been previously studied in superficial BCC. McKay et al. a mean tumor thickness of 0.3 mm (range: 0.09–1.41) (16). The authors found that a tumor thickness greater than 0.40 mm is an indicator of treatment failure following topical imiquimod therapy (recurrence rate: 58%) [12].

Although we did not find a significant relationship between various parameters and depth of invasion in our study, specifying the depth of invasion in pathology reports may be important for surgical procedure and topical treatment in patients who cannot undergo extensive surgical resection. According to its localization, BCC can cause significant morbidity, especially in areas such as the periocular region where surgical intervention is limited. The depth of invasion may be clinically silent, so identifying the depth of invasion may also alert clinicians to the possibility of inadequate excision. A progressive increase in the incidence of BCC is noted making it an occupational and environmental disease with an obvious impact on the life quality of the patients. This puts a notable burden on the healthcare system, particularly in cases of invasive treatments and post-treatment relapses. Conducting multicenter research that investigates the efficacy of depth of invasion in different anatomical locations in a higher number of cases may help develop more effective treatments.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
There is no financial support.

Ethical approval
The study was approved by KTO Karatay University, Ethics Committee of Research with Non-Pharmaceutical Products and Non-Medical Devices (approval number:2021/025).

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